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10/581,580	03/29/2007	Shyam S. Mohapatra	USF-208TCXC1	6999

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SALIWANCHIK LLOYD & SALIWANCHIK
A PROFESSIONAL ASSOCIATION
PO Box 142950
GAINESVILLE, FL 32614

EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	PAPER NUMBER
1635	

NOTIFICATION DATE	DELIVERY MODE
09/18/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

euspto@slspatents.com

Office Action Summary	Application No.	Applicant(s)	
	10/581,580	MOHAPATRA ET AL.	
	Examiner	Art Unit	
	Richard Schnizer	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 July 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31* is/are pending in the application.

4a) Of the above claim(s) *1-11 and 27-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 June 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/15/08;4/17/09;7/28/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

An amendment was received and entered on 7/28/09. Applicant's election without traverse of Invention 5 is acknowledged. After further consideration, the restriction requirement between groups 4 and 5 is withdrawn. Note also that claim 20 was inadvertently omitted from any group, and should have been included with the elected invention.

Claims 1-11 and 27-31 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 7/28/09.

Claims 12-26 are under consideration in this Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 25 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 25 is indefinite because it indicates that surfactant protein B is a regulatory sequence that can be operably linked to a polynucleotide. Surfactant protein B is a polypeptide, not a regulatory sequence that can be operably linked to a polynucleotide.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 12, 13, 16-18, 22, and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Leaman et al (Virology 292: 70-77, 1/2002).

Leaman taught a method of treating RSV infection in African green monkeys by nasal instillation of an antisense oligonucleotide directed against RSV RNA. The treatment reduced nasal RSV replication by up to 10000-fold. See abstract. Delivery to respiratory epithelial cells is considered to be inherent in intranasal instillation. The expression of all RSV polypeptides, including NS1, NS2, and any RSV polypeptide that reduces type-I interferon expression, is considered to have been reduced because the titer of the virus was reduced 10000-fold. If there is less virus, there is necessarily less expression of all viral proteins.

Thus Leaman anticipates the claims.

Claims 12, 13, 15, 17-19, 22, and 26 rejected under 35 U.S.C. 102(b) as being anticipated by Torrence et al (US 5,998,602).

Torrence taught methods of treating RSV infection humans by inhalation of an aerosol comprising an antisense oligonucleotide directed against RSV RNA. See abstract; column 1, lines 9-12; and paragraph bridging columns 2 and 3. Delivery to

respiratory epithelial cells is considered to be inherent in intranasal instillation. The expression of all RSV polypeptides, including NS1 and NS2 which reduce type-I interferon expression, is considered to have be inherent in reduction of virus titer. If there is less virus, there is necessarily less expression of all viral proteins.

Thus Torrence anticipates the claims.

Claims 12, 13, 15-18, 22-24, and 26 rejected under 35 U.S.C. 102(b) as being anticipated by McSwiggen et al. (US Patent 5,693,532).

McSwiggen taught methods of inhibiting the replication of RSV in vivo through use of specific ribozymes targeted to RSV mRNA for treatment of diseases in man and other animals. The ribozymes are targeted to NS1 and NS2 targets which reduce type-I interferon expression in cells. See columns 2-3, for example. Absent evidence to the contrary this would result in a relative increase in type I interferon expression. Preferred administration is by aerosol inhalation (see column 9, lines 8-16). The ribozymes can be expressed from vectors (column 5, lines 10-12 and 27-52. Ribozymes can also be administered by nanocapsule.

Thus McSwiggen anticipates the claims.

Claims 12, 13, 15, 20, 22-24, and 26 rejected under 35 U.S.C. 102(b) as being anticipated by Barik (US 5,831,069).

Barik taught methods of killing human respiratory syncytial virus in an individual in need of such treatment, comprising the step of contacting said virus with an effective

dose of the oligonucleotide of the present invention. The oligonucleotide is preferably targeted to NS1 or NS2 targets which reduce type-I interferon expression in cells. Absent evidence to the contrary this would result in a relative increase in type I interferon expression. The oligonucleotides can be administered alone or in combination. See abstract, column 4, line 47 to column 5, lines 3-19.

Thus Barik anticipates the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 12-19, 22-24, and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over McSwiggen et al (US Patent 5,693,532).

McSwiggen taught methods of inhibiting the replication of RSV in vivo through use of specific ribozymes targeted to RSV mRNA for treatment of diseases in man and other animals. The ribozymes are targeted to NS1 and NS2 targets which reduce type-I interferon expression in cells. See columns 2-3, for example. Absent evidence to the contrary this would result in a relative increase in type I interferon expression. Preferred administration is by aerosol inhalation (see column 9, lines 8-16). The ribozymes can be expressed from vectors (column 5, lines 10-12 and 27-52. Ribozymes can also be

administered by nanocapsule. Thus McSwiggen anticipates and renders obvious claims the claims 12, 13, 15-18, 22-24, and 26.

McSwiggen did not teach administration to a subject not suffering from RSV infection as required by instant claim 14 or intranasal delivery as required by instant claim 19.

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer the ribozymes of McSwiggen to a subject not suffering from RSV infection in at least two instances. First, in any experiment in which such ribozymes are administered to individuals infected with RSV, administration of ribozymes to an individual not suffering from RSV infection would serve as a control on the effects of the ribozymes on the individual in the absence of any confounding effects of viral infection. This would clearly be of interest to those of ordinary skill in the art wishing to assess or establish the safety of the treatment. Second, it would be obvious to administer the ribozymes to individuals that are not suffering from RSV infection, but that are about to be exposed to RSV. One would be motivated to do so in order to prevent infection.

Regarding intranasal administration, McSwiggen taught administration by aerosol inhalation. There are two possible routes for this administration, oral and nasal, each of which is considered to be an obvious variant of the other.

Thus the invention as a whole was prima facie obvious.

Claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over McSwiggen et al (US Patent 5,693,532) as applied to claims 12-19, 22-24, and 26 above, and further in view of Tuschl et al. (US 20040259247 A1) and Leaman et al (Virology 292: 70-77, (2002)).

McSwiggen taught methods of inhibiting the replication of RSV in vivo through use of specific ribozymes targeted to RSV mRNA for treatment of diseases in man and other animals (see columns 2-3, for example). Preferred administration is by aerosol inhalation (see column 9, lines 8-16).

McSwiggen did not teach an siRNA.

Leaman taught targeted therapy of RSV infection in African green monkeys through intranasal instillation of 2-5 adenosine linked antisense oligonucleotides directed against RSV genomic RNA. See abstract; page 74, first full paragraph, and Fig. 2 on page 74. Thus Leaman taught that antisense oligonucleotides directed to RSV could be successfully delivered intranasally to target RSV in vivo.

Tuschl taught methods and materials for making and using short, double stranded interfering RNAs (siRNAs) against virtually any known gene for both research and clinical use. It is said the target gene to which the RNA molecule of the invention is directed may be a viral gene associated with a pathological condition (paragraph 30). The siRNAs consist of sense and antisense strands of between 19 and 25 nucleotides in length, wherein the antisense strand is complementary to a target gene (cols. 1-3).

Tuschl taught and/or suggested both in vitro transfection and in vivo delivery of siRNAs for therapeutic purposes (pages 3-4, and see examples).

Thus, Tuschl provided a general blueprint for the design, synthesis, and application of short interfering RNAs.

Importantly, Tuschl also directly compared and contrast ribozyme and RNAi technologies, stating at paragraph 148 that "...siRNAs are extraordinarily powerful reagents for mediating gene silencing and that siRNAs are effective at concentrations that are several orders of magnitude below the concentrations applied in conventional antisense or ribozyme gene targeting experiments."

Accordingly, Tuschl provided general art-accepted motivation and enabling disclosure for making and using chemically modified siRNAs against known genes associated with pathogenic conditions.

It would have been obvious to one of ordinary skill in the art at the time of the invention to make and use siRNAs of 19–25 nucleotides in length, complementary to and capable of inhibiting the expression of an RSV mRNA. One of skill would have been well motivated and have had a reasonable expectation of success given that the combination of cited prior art references as a whole taught and/or suggested that ribozymes and antisense targeted to RSV mRNA would provide for inhibition of RSV in vitro and in vivo. Given that Leaman demonstrated that antisense RNA directed to RSV could be delivered intranasally in vivo to therapeutic effect, one of skill would have reasonably expected that siRNAs targeted to RSV could be successfully delivered in vivo as well. One of skill would have been motivated to substitute siRNAs for the

ribozymes disclosed by McSwiggen given that Tuschl taught that siRNAs are in general significantly more potent than ribozymes.

Thus the invention as a whole was prima facie obvious.

Claim 25 is under 35 U.S.C. 103(a) as being unpatentable over McSwiggen et al (US Patent 5,693,532) as applied to claims 12-19, 22-24, and 26 above, and further in view of Prince et al (US 5,290,540) and Huang et al (US 6,586,579).

McSwiggen taught methods of inhibiting the replication of RSV in vivo through use of specific ribozymes targeted to RSV mRNA for treatment of diseases in man and other animals. The ribozymes are targeted to NS1 and NS2 targets which reduce type-I interferon expression in cells. See columns 2-3, for example. Absent evidence to the contrary this would result in a relative increase in type I interferon expression. Preferred administration is by aerosol inhalation (see column 9, lines 8-16). The ribozymes can be expressed from vectors (column 5, lines 10-12 and 27-52.

McSwiggen taught that eukaryotic pol I, pol II, or pol III promoters could be used to drive expression of ribozymes, and that the levels of a given pol II promoter in a given cell type will depend on the nature of the gene regulatory sequences used, such as enhancers. See column 9, lines 17-27.

McSwiggen did not teach a polynucleotide comprising a regulatory sequence that is a steroid response element.

Prince taught a method of treating RSV infection by aerosol topical application to the respiratory tract of an anti-viral agent and an anti-inflammatory steroid. See column 1, lines 26-38; paragraph bridging columns 6 and 7; column 7, lines 15-22; and claim 7.

In view of the suggestion of Prince to treat RSV infection by combining steroid treatment with administration of antivirals, it would have been obvious to one of ordinary skill in the art at the time of the invention to modify the antiviral treatment of McSwiggen (i.e. inhalation of expression vectors encoding anti-RSV ribozymes) by combining it with the use of a steroid applied to the lung.

These combined references do not teach the use of a steroid response element as an expression control sequence in the expression vector.

Huang taught that the use of inducible gene expression is advantageous, and that an exemplary inducible expression control element is a steroid response control element. See column 14, lines 13-16 and 22-25.

The selection of expression control sequences for an expression vector is considered to be a matter of design choice, such that the use of any expression control sequence that could function in the desired environment would be obvious absent evidence of secondary considerations. Further, in view of the teachings of Huang, one of ordinary skill in the art at the time of the invention clearly appreciated that inducible control of expression was beneficial, and that steroid responsive induction of gene expression was available. Accordingly, it would have been obvious to one of ordinary skill in the art at the time of the invention to use a steroid inducible element to modulate expression of the ribozyme in the method of McSwiggen as modified by Prince,

because the combined methods call for the use of steroids in the lung, and one of ordinary skill would clearly perceive that a steroid response element would allow the controllable induction of anti-viral ribozyme expression, thereby advantageously allowing combination of the anti-inflammatory steroid effect with the antiviral ribozyme effect.

Thus the invention as a whole was prima facie obvious.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, James (Doug) Schultz, can be reached at (571) 272-0763. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

/Richard Schnizer/
Primary Examiner, Art Unit 1635